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Does hydroxychloroquine combat COVID-19? A timeline of evidence



To the Editor: Chloroquine (CQ) and hydroxychloroquine (HCQ) garnered scientific attention in early February after publication of reports showing in vitro activity of CQ against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19.¹ On February 17, 2020, the State Council of China held a news conference indicating that chloroquine (CQ) had demonstrated efficacy in treating COVID-19-associated pneumonia in multicenter, nonrandomized, clinical trials.^{2,3} This prompted multiple clinical trials in China (9 as of April 3, 2020).⁴ Gao et al⁵ treated >100 patients with CQ, reporting control in inhibiting the exacerbation of pneumonia, improved lung imaging findings, and shortened disease course, but detailed data underlying the claims have not yet been published.

Hydroxychloroquine (HCQ), an analogue of CQ with fewer side effects, better safety profile, and less drug interactions, showed in vitro antiviral activity against SARS-CoV in the previous SARS outbreak.⁵ Yao et al⁶ compared the in vitro anti-SARS-CoV-2 activity of both drugs, finding HCQ superior to CQ and recommending HCQ sulfate 400 mg twice daily on day 1, followed by 200 mg twice daily for the next 4 days to treat COVID-19. Similar in vitro results were reported by the Wuhan Institute of Virology.⁷ As the epicenter of COVID-19 shifted from China to Europe, Colson et al^{8,9} recommended use of HCQ as a possible prophylaxis and curative treatment for COVID-19.

Gautret et al¹⁰ were the first to report promising in vivo data of HCQ in a nonrandomized clinical trial. They used 200 mg of HCQ 3 times a day for 10 days, plus azithromycin if deemed necessary. A higher frequency of SARS-CoV-2 clearance was noticed after 6 days of treatment with HCQ alone or HCQ plus azithromycin vs the untreated control group (70% vs 12.5%; $P < .001$). Azithromycin added to HCQ was significantly more efficient for virus

elimination. These findings were rapidly disseminated by the lay press and social media, leading to endorsement of HCQ by many government and institutional leaders, including President Trump, who referred to this as a “game changer.” The demand for HCQ increased exponentially, leading to an overall shortage and making prescription refills challenging.^{11,12}

On March 31, 2020, [medRxiv.org](https://www.medrxiv.org) published data of the first completed randomized clinical trial in Wuhan investigating the efficacy of HCQ in patients with COVID-19.¹³ The trial randomized 62 patients equally into 2 groups. The treatment group received oral HCQ 400 mg/d (200 mg twice daily) from day 1 to 5. Their article, currently under revision, reported a significant difference in the time to clinical recovery and radiologic findings between the groups (Table I).¹³

To date, despite enough rationale to justify investigation into the efficacy and safety of HCQ in COVID-19 (Table II),^{14,15} the evidence regarding its effect remains limited. HCQ has not yet received United States Food and Drug Administration approval for use against COVID-19, and further trials are needed to establish guidelines. If emerging data from ongoing trials establishes the efficacy of HCQ for prophylaxis and treatment of COVID-19, triage will be important to ensure that existing supplies are used appropriately.

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Table I. Summary of the findings on the first randomized trial using hydroxychloroquine against COVID-19¹³

End points	Treatment arm	Control arm
Body temperature recovery time, d*	2.2	3.2
Cough remission, d*	2	3.1
Chest computed tomography results improvement, %*†	80.6	54.8

*Results are statistically significant.

†Comparing results on day 0 and day 6.

Table II. Summary of the antiviral mechanism of action of chloroquine and hydroxychloroquine^{14,15}

Mechanism	Effect
Halts the glycosylation of ACE2R	Reduces binding of spike protein of coronavirus to ACE2R on host cell
Increases the endosomal and lysosomal pH	Prevents fusion of the virus with host cells and subsequent replication
Prevents antigen processing and MHC-II-mediated autoantigen presentation to T cells	Reduces T-cell activation and expression of CD154 and other cytokines (IL-1, IL-6 and TNF- α)
Disrupts the interaction of cytosolic viral DNA/RNA with TLRs and the nucleic acid sensor cGAS*	Halts transcription of proinflammatory genes attenuating the possibility of cytokine storm (type I interferons, IL-1, TNF- α)

ACE2R, Angiotensin-converting enzyme 2 receptor; cGAS, cyclic guanosine monophosphate- adenosine monophosphate synthase; IL, interleukin; MHC, major histocompatibility complex; TLR, Toll-like receptor; TNF, tumor necrosis factor.

*Hydroxychloroquine only.

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